Remarks

Claims 1-138 are pending. Claims 137 and 138 were previously withdrawn from consideration as being drawn to a non-elected invention. Claims 1, 107, 108, 110, 124, 133, 134, 135, and 136 have been amended to more clearly define what applicants claim as the invention and to address questions Applicants have about Examiner Chunduru's understanding of the present claims.

Claims 1, 107, 108, and 110 were amended to recite "bringing into contact the decoupled amplification target circles and one or more rolling circle replication primers". Support for the amendments can be found at least in Figure 3 as well as the description of Figure 3 on page 7, lines 22-30. Support can also be found at least on page 10, lines 16-17 where replication of amplification target circles after decoupling is described.

Claims 124, 133, 134, 135, and 136 were amended to recite "replicating the decoupled amplification target circles". Support for the amendments can be found at least in Figure 3 as well as the description of Figure 3 on page 7, lines 22-30. Support can also be found at least on page 10, lines 16-17 where replication of amplification target circles after decoupling is described.

Applicants attempted to contact Examiner Chunduru, but were informed that Examiner Chunduru would not return to the Office until May 2, after the next due date for response. Applicants then contacted Examiner Benzion to discuss Applciants' options. Examiner Benzion suggested that Applicants file the present Response and contact Examiner Chunduru after she returns to discuss the claims. Examiner Benzion suggested that a supplemental Response could be filed soon thereafter if the conversation with Examiner Chunduru provided useful insights to advance prosecution. Examiner Benzion suggested that such a Supplemental Response would be given consideration if it was filed soon after the conversation with Examiner Chunduru.

Double Patenting Rejection

Claims 1-136 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 6,921,642 to Kingsmore et

al in view of Baner et al (Nucleic Acids Res. vol 26, pages 5073-5078 (1998)). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Applicants note that in an obviousness-type double patenting rejection the question is not whether claims of one application *encompass* those of another, but rather whether the claims of one application are *obvious* in view of the claims of another application. Generally, the analysis required to show such obviousness is the same the analysis required to show obviousness under 35 U.S.C. § 103 (*In re Braithwaite,* 379 F.2d 594, n.2 (CCPA 1967)). Thus, the question is whether it would have been obvious to modify the methods or compositions claimed in the application and the patent to arrive at what is presently claimed.

When considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. *General Foods Corp. v. Studiengesellschafi Kohle mbH*, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1846 (Fed. Cir. 1992).

Claims 1, 107, 108, 110, 124, and 133-136, as well as all the claims dependent there from, are directed to methods of detecting one or more analytes. Each of the claims require specific compositions that interact together as well as a specific order in which each of the required interactions take place. Specifically, the claims require the use of reporter binding molecules. As claimed, the reporter binding molecules comprise a specific binding molecule and an amplification target circle. That is, the claimed reporter binding molecules specifically include as a component an amplification target circle. After the specific binding molecule portion of the reporter binding molecule interacts with its cognate analyte, the amplification target circle that is part of that reporter binding molecule is decoupled from the specific binding molecule. Only after the amplification target circle is decoupled from the specific binding molecule, is a rolling circle replication primer introduced and hybridized to the decoupled amplification target circle. Then, and only after the amplification target circle is decoupled from the specific binding molecule (which interacts with the analyte), is the amplification target circle replicated. In other words, the amplification target circle is not associated with the analyte-specific binding molecule composition when it is replicated. Thus, the claims require at least (1) a reporter binding molecule that includes both a specific binding molecule (that can interact with

an analyte) and an amplification target circle, (2) decoupling of that amplification target circle associated with the analyte from that specific binding molecule, (3) bringing into contact the decoupled amplification target circles and one or more rolling circle replication primers, and (4) replication of the decoupled amplification target circle.

Claims 1-36 of Kingsmore et al. are drawn to methods for detecting analytes involving bringing analytes into contact with reporter binding primers. The reporter binding primers disclosed by Kingsmore et al. comprise a specific binding molecule and a rolling circle replication primer. The analytes are brought into contact with the reporter binding primers in such a way that the specific binding molecule binds to the analyte. Once the specific binding molecule of the reporter binding primer binds to the analyte, an amplification target circle is brought into contact with the rolling circle replication primer (which is part of the reporter binding primer) and the amplification target circle is replicated via priming by the rolling circle replication primer, thus forming tandem sequence DNA. As such, the replication of the amplification target circle takes place in such a way that the amplification target circle remains associated with the analyte as it is replicated, thus the TS-DNA formed also remains associated with the analyte. The Office Action admits on page 3, line 22- page 4, line 2, that Kingsmore et al. fails to teach or suggest decoupling of an amplification target circle associated with analytes from a specific binding molecule. In addition, Kingsmore et al. fails to teach or suggest the claimed reporter binding molecule (a combination of a specific binding molecule and an amplification target circle). In fact, in the claimed methods of Kingsmore et al., the amplification target circle is associated with the reporter binding primer (via the rolling circle replication primer) prior to replication and remains associated with the reporter binding primer during replication (see the bottom panels of Figure 1 where the amplification target circle is shown at the growing tip of the replicated strand as well as Figures 11, 13 and 14).

Baner et al. discloses padlock probes and their potential uses to detect sets of gene sequences with high specificity and selectivity for sequence variants. In order for the reaction of Baner et al. to take place, the linear oligonucleotides (un-circularized padlock probes) must itself first hybridize to their target, then, if properly hybridized, the 5' and 3' ends of the linear oligonucleotides can be joined by enzymatic ligation, thus converting the probes into circularly

closed molecules that are concatenated to the target. The circularly closed molecules (padlock probes) can then be subjected to rolling circle replication. Baner et al. also discloses that to increase the efficiency of the rolling circle replication of the padlock probes, the topological link formed between the padlock probe and its target sequence can be removed, however, the methods disclosed by Baner et al. all require initiation of rolling circle replication prior to the release of the padlock probe from the target sequence. In other words, the rolling circle replication primer is brought into contact with the padlock probe prior to release of the padlock probe from its target sequence. Baner et al. also fails to disclose or suggest a reporter binding molecule comprising a specific binding molecule and an amplification target circle. Applicants further submit that Baner et al. fails to disclose or suggest the decoupling of amplification target circles from their associated specific binding molecules prior to replication of the amplification target circles.

First, the Office Action again alleges that the claims of Kingsmore et al. teach the claimed reporter binding molecule. The Office Action fails to specifically point out where Kingsmore et al. teaches such a composition, to wit Applicants submit is impossible as nowhere in Kingsmore et al. is such a composition taught or suggested. To support its conclusion, the Office Action attempts to rely on two misguided theories: (1) that due to the use of the term "comprising" the pending claims are open and (2) that because Kingsmore et al. discloses that the steps of claim 1 of Kingsmore et al. broadly encompass that the steps can be performed in any order, that Kingsmore et al. broadly encompasses the compositions and methods of the currently pending claims. Both theories are simply incorrect. Applicants submit that the Office Action has simply overlooked the requirement that in the currently pending claims, rolling circle replication primers are not brought into contact with an amplification target circle, until the amplification target circle is decoupled from its cognate specific binding molecule. In each and every claim of Kingsmore et al., the rolling circle replication primer is brought into contact with an amplification target circle, thus coupling the ATC indirectly with an analyte via a reporter binding primer. Applicants again remind the Examiner that a reporter binding primer comprises a specific binding molecule and a rolling circle replication primer, thus even if the reporter binding primer further comprised an amplification target circle, the overall composition would then

comprise a rolling circle replication primer and an amplification target circle coupled to a specific binding molecule. In other words, the primer of Kingsmore et al. would **not be added after** the amplification target circle was decoupled from the specific binding molecule, rather the ATC must be coupled to the specific binding molecule in the method of Kingsmore et al.or otherwise it **can not** be replicated. The present claims make it clear that the amplification target circle must be decoupled from its cognate specific binding molecule before a primer is added AND that replication does not take place until after the decoupling step.

Baner et al. which was cited for teaching releasing a padlock probe from the link that forms with target molecules upon hybridization and ligation, fails to supplement the missing elements from Kingsmore et al. Specifically, Baner *et al.* fails to teach or suggest (1) a reporter binding molecule that comprises both a specific binding molecule (that can interact with an analyte) and an amplification target circle. In fact, Applicants submit that the Office Action does not cite Baner et al. for teaching or suggesting the claimed reporter binding molecules. As such, since neither Kingsmore et al. nor Baner et al. teach or suggest one of the required compositions, it is impossible for the two to teach or suggest decoupling of that amplification target circle associated with the analyte from it cognate specific binding molecule.

In addition to the failures of Baner et al. regarding the claimed compositions, Baner et al. also fails to teach or suggest bringing into contact a decoupled amplification target circle and one or more rolling circle replication primers. As discussed above, Baner et al. teaches the use and replication of padlock probes. Padlock probes, as disclosed by Baner et al., are oligonucleotide probes capable of hybridizing to a target nucleic acid sequence, and upon hybridizing can be circularized. Thus, in order for padlock probes to be circularized, they must bind directly to a target sequence or, as Baner et al. provides on column 2 of page 5073, the padlock probes must form a topological link with its target. What Baner et al. goes on to discuss is the fact that if the padlock probe is released from this topological link, rolling circle replication can take place more efficiently. While it is true that Baner et al. does disclose releasing the padlock probe from the topological link that forms with a target molecule, the replication begins with the padlock probe still topologically linked to the target. The mechanism disclosed by Baner et al. requires that the replication machinery all be present while the padlock probe is topologically linked to the target.

It is only once replication begins that the polymerase dissociates the circularized padlock probe from the target. In other words, a primer has to hybridize to the padlock probe, the polymerase has to begin replication, and a synthesized strand must be generated before the padlock probe dissociates fro the target. (See Baner et al. page 5076, column 2 last paragraph as well as Figure 5). Figure 5 distinctly illustrates and the figure legend specifically provides that polymerization takes place at the 3' end of the primers (previously hybridized to the padlock probe) and that once the primers are extended, the padlock probe is displaced from the target. Put simply, the primers are brought into contact with the coupled padlock probe and replication of the padlock probes occurs with the padlock probe still coupled to the target. Thus, Baner et al. not only fails to supplement the missing elements from Kingsmore et al., specifically a reporter binding molecule that comprises both a specific binding molecule (that can interact with an analyte) and an amplification target circle, Baner et al. also fails to teach or suggest bringing into contact a decoupled amplification target circles and one or more rolling circle replication primers.

Applicants therefore submit that Kingsmore et al. and Baner et al. fail to teach or suggest (1) a reporter binding molecule that comprises both a specific binding molecule (that can interact with an analyte) and an amplification target circle, (2) bringing into contact a decoupled amplification target circles and one or more rolling circle replication primers, and (3) the decoupling of amplification target circles from their associated specific binding molecules prior to replication of the amplification target circles. As such, Applicants further submit that Kingsmore et al. and Baner et al., either alone or in combination, fail to disclose or suggest every feature of the claims. Accordingly, for at least these reasons, Kingsmore et al. and Baner et al. fail to make obvious claims 1-136.

Even if, one of skill in the art were to accept the Office Action's allegation that Baner et al. teaches decoupling of an amplification target circles associated with an analyte from the specific binding molecule associated with the same analyte, Applicant's submit that it would not be obvious to one of ordinary skill in the art to combine such a teaching with the teachings of Kingsmore et al. The Office Action alleges (page 8, lines 1-6) that one of skill in the art would have been motivated to combine Baner et al. and Kingsmore et al. based on Baner et al.'s alleged teaching of using circularized probes to yield a powerful signal amplification by releasing the

link that forms between the circular probe and the target sequence (which Applicants rebut above). Applicants reject the Office Action's allegation and submit that one of ordinary skill in the art would not have been motivated to combine the references of Kingsmore et al. and Baner et al. as suggested by the Office Action because modification of the method of Kingsmore et al. cited in the rejection as suggested in the rejection would change the principle of operation of the method and thus the present rejection cannot be sustained.

The current rejection cannot be sustained if the proposed modification would alter the fundamental principle of operation of the prior art to be modified. *In re Ratti*, 270 F.2d 810, 813, 123 USPQ 349(CCPA 1959). Modification of the method of Kingsmore et al. cited in the rejection as suggested in the rejection would change the principle of operation of the method and thus the present rejection cannot be sustained.

As provided above, Kingsmore et al. discloses a method for detecting analytes involving bringing analytes into contact with reporter binding primers, which are made up of a specific binding molecule and a rolling circle replication primer, such that the specific binding molecule binds to the analyte. An amplification target circle is brought into contact with the rolling circle replication primer (which is part of the reporter binding primer) and the amplification target circle is replicated via priming by the rolling circle replication primer, thus forming tandem sequence DNA. In the method of Kingsmore et al. the amplification target circle is associated with the reporter binding primer (via the rolling circle replication primer) prior to replication and remains associated with the reporter binding primer during replication.

In fact, if the amplification target circle was dissociated from the reporter binding primer prior to replication, as suggested by the Office Action, the amplification target circle could not be replicated because such dissociation would separate the amplification target circle from the rolling circle replication primer (the primer is part of the reporter binding primer). Further, even if such a hypothetical dissociated amplification target circle was replicated using a different primer, this would defeat Kingsmore et al.'s purpose in having a rolling circle replication primer as part of a reporter binding primer. Kingsmore et al. states that:

> The method involves associating nucleic acid primer with the analyte and subsequently using the primer to mediate rolling circle replication of a circular

> DNA molecule. Amplification of the DNA circle is dependent on the presence of the primer. Thus, the disclosed method produces an amplified signal, via rolling circle amplification, from any analyte of interest. The amplification is isothermic and can result in the production of a large amount of nucleic acid from each primer. The amplified DNA remains associated with the analyte, via the primer, and so allows spatial detection of the analyte.

Column 4, lines 37-47 (emphasis added).

Dissociation of the amplification target circle would eliminate the intended connection between the analyte and the amplified DNA and thus eliminate the spatial detection of the analyte sought by Kingsmore et al. This alteration, required by the present rejection, would eliminate a major feature of the method of Kingsmore et al. Such a change in the principle of operation of the method of Kingsmore et al., which results from the modification proposed by the rejection, renders the rejection unsustainable. Accordingly, Kingsmore et al. and Baner et al. fail to make obvious the method of claims 1-136.

For all the reasons above, Kingsmore et al. and Baner et al., either alone or in combination, fail to disclose or suggest every feature of the claims. In addition, one of ordinary skill in the art would not be motivated to combine Kingsmore et al. and Baner et al. because such a combination would alter the fundamental principle of operation of Kingsmore et al.. Accordingly, Kingsmore et al. and Baner et al. fail to make obvious claims 1-136.

Pursuant to the above remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

No fees are believed due. However, the Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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